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JAPANESE PATENT APPLICATION (A)

No. J62-158252

4-AMINOPYRIDINE BENZAMIDE DERIVATIVES

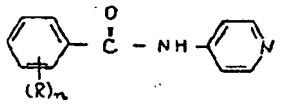
Specification

1. Title of invention

4-aminopyridine benzamide derivatives.

2. Sole patent claim

4-aminopyridine benzamide derivatives containing formula (I) or a pharmaceutically acceptable salt thereof.



(I)

(in the formula, R denotes hydrogen atom, halogen atom, lower alkoxy, lower alkyl, nitro, cyano or di-lower alkylamino, n denotes 1, 2 or 3. Wherein, when n is 2 or 3, each R may be the same or different. The position of R is any one of 2', 3', 4', 5' or 6', or combinations of plurality of these).

3. Detailed Description of the Invention.

Background of the invention

This invention relates to 4-aminopyridine benzamide derivatives. The said compound has a cardiotonic action.

Outline of the invention

This invention relates to a novel compound, and the said novel compound is a 4-aminopyridine benzamide derivative containing the following formula (I) or a pharmaceutically acceptable salt thereof.

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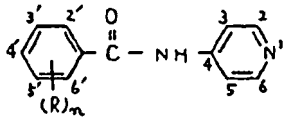
Detailed Description of the Invention

A compound and a production thereof

The novel 4-aminopyridine benzamide derivatives in accordance with this invention is represented by formula (I).



(I)

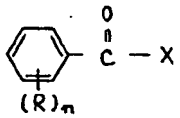
(in the formula, R denotes hydrogen atom, halogen atom, lower alkoxy, lower alkyl, nitro, cyano or di-lower alkylamino, n denotes 1, 2 or 3. Wherein, when n is 2 or 3, each R may be the same or different. The position of R is any one of 2', 3', 4', 5' or 6', or combinations of plurality of these).

The halogen atom used here is typically chlorine, bromine or fluorine, and the "lower" denotes the carbon number of around 1-4. Accordingly, the actual example of lower alkoxy is methoxy, the actual example of lower alkyl is methyl or t-butyl, and the actual example of lower di-alkylamino is dimethylamino.

The pharmaceutically acceptable salts of the compound of formula (I) are included in the range of this invention. Examples of such salts include for example inorganic acid salt such as hydrochloride, sulphate or the like, and organic acid salt such as citrate, maleate, fumarate, benzoate, succinate, acetate, tartrate or the like.

The compound of formula (I) can be conveniently produced by applying well known methods. For example, there are following methods.

(1) A method wherein an acid halide having formula (II) is reacted with 4-aminopyridine in the co-presence of base.



(II)

The explanations of R and n are the same as in formula (I), X denotes chlorine or bromine.

(2) A method wherein a carboxylic acid having formula (III) is reacted with 4-aminopyridine in the co-presence of a suitable onium salt for example 2-chloro-1-methylpyridinium iodide and a suitable base for example triethylamine (Chem. Lett., 1163 (1975)).

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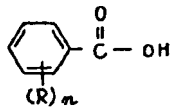
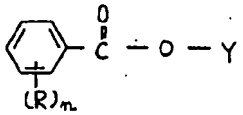


(III)

The explanations of R and n are the same as in formula (I).

(3) A method wherein the same carboxylic acid having formula (III) is reacted with 4-aminopyridine in the co-presence of a suitable condensing agent for example dicyclohexylcarbodiimide.

(4) A method wherein a mixed acid anhydride having formula (IV) that can be prepared by a suitable method from the same carboxylic acid having formula (III) is reacted with 4-aminopyridine.



(IV)

The explanations of R and n are the same as in formula (I), Y denotes alkylcarbonyl, ethoxycarbonyl (J. Med. Chem., 11, 534, (1968)), 4-toluenesulphonyl (J. Am. Chem. Soc., 77, 6214, (1955)), 1,2-phenylene dioxyboryl (J. Organic. Chem., 43, 4393 (1978)) or trifluoroacetyl triphenylphosphonyl (Tet. Lett., 277 (1975)).

(5) A method wherein the same carboxylic acid having formula (III) is reacted with 4-aminopyridine in the co-presence of a suitable trialkyl phoephine for example tributyl phosphine or the like and 2-nitrobenzene sulenyl cyanide (J. Organic. Chem., 44, 2945, (1979)).

Representative examples of the compounds of the aforesaid formula (I) put forward by this invention are as follows.

N-benzoyl-4-aminopyridine, N-(2'-chlorobenzoyl)-4-aminopyridine, N-(3'-chlorobenzoyl)-4-aminopyridine, N-(4'-chlorobenzoyl)-4-aminopyridine, N-(2'-bromobenzoyl)-4-aminopyridine, N-(3'-bromobenzoyl)-4-aminopyridine, N-(4'-bromobenzoyl)-4-aminopyridine, N-(2'-fluorobenzoyl)-4-aminopyridine, N-(3'-fluorobenzoyl)-4-aminopyridine, N-(4'-fluorobenzoyl)-4-aminopyridine, N-(3'-methoxybenzoyl)-4-aminopyridine, N-(4'-methoxybenzoyl)-4-aminopyridine, N-(2'-methylbenzoyl)-4-aminopyridine, N-(3'-methylbenzoyl)-4-aminopyridine, N-(4'-methylbenzoyl)-4-aminopyridine, N-(4'-nitrobenzoyl)-4-aminopyridine, N-(4'-cyanobenzoyl)-4-aminopyridine, N-(4'-t-butylbenzoyl)-4-aminopyridine, N-[4'-(N',N'-dimethylamino) benzoyl]-4-aminopyridine, N-(2',4',5'-trimethoxybenzoyl)-4-aminopyridine, N-(3',4'-dimethoxybenzoyl)-4-aminopyridine, N-(2',6'-dichlorobenzoyl)-4-aminopyridine, N-(2',6'-dimethoxybenzoyl)-4-aminopyridine, or the like.

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Usefulness of the compounds of this invention

The 4-aminopyridine benzamide derivatives of formula (I) and salts thereof in accordance with this invention have myocardial contraction increasing action, and are useful as congestive cardiac insufficiency therapeutic agent and as cardiac stimulant.

When the 4-aminopyridine benzamide derivatives of formula (I) and salts thereof in accordance with this invention are used as drugs, the agent can be formulated into forms such as capsule, tablet, injection or the like using non-toxic excipient, diluent or carrier usually used in this type of drugs.

The dosage of the compound of this invention can be widely altered according to the target human or species of other mammals, administration route, severity of the symptoms, diagnosis by the physician or the like, however, in the case of oral administration, generall the dose of 0.1-10 mg/kg per day, more preferably, 0.3-3 mg/kg.

Examples

Synthesis of the compounds

In the Examples, the temperature is in centigrade in each case, and the melting point is not corrected. The NMR measurement was carried out using tetramethylsilane as internal standard, and is shown in ppm.

Example 1

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent made of chloroform (50 ml) and acetonitrile (50 ml), thereto was drowpwise added benzoyl chloride (1.40 g), and the mixture was stirred at room temperature for 30 minutes. Thereto was added 10 % potassium carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. The chloroform layer was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was re-crystallised from chloroform–n-hexane, and N-benzoyl-4-aminopyridine (1.82 g) was obtained.

mp: 202-203° (re-crystallised from chloroform–n-hexane).

IRν^{KBr}_{max} (cm^{-1}): 1680, 1590.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 7.48-7.66 (m, 5H), 7.81-7.94 (m, 2H), 8.06 (s, 1H), 8.48-8.61 (m, 2H).

Elemental analysis:	Calculated (as $C_{12}H_{10}N_2O$)	C: 72.71, H: 5.09, N: 14.13
	Measured value	C: 72.56, H: 5.02, N: 13.92

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Example 2

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent made of chloroform (50 ml) and acetonitrile (50 ml), thereto was added 2-chlorobenzoyl chloride (1.75 g), and the mixture was stirred at room temperature for 30 minutes. Thereto was added 10 % potassium carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. The chloroform layer was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was re-crystallised from chloroform–n-hexane, and N-(2'-chlorobenzoyl)-4-aminopyridine (2.12 g) was obtained.

mp: 168-169° (re-crystallised from chloroform–n-hexane).

IRν^{KBr}_{max} (cm^{-1}): 1690, 1590.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 7.25-7.72 (m, 6H), 8.34-8.46 (m, 2H), 9.18 (s, 1H).

Elemental analysis:	Calculated (as $C_{12}H_9N_2ClO$)	C: 61.94, H: 3.90, N: 12.04
	Measured value	C: 61.82, H: 3.83, N: 11.88

Example 3

3-chlorobenzoic acid (1.56 g), triphenyl phosphine (3.93 g) and carbon tetrabromide (5.32 g) were dissolved in methylene chloride (30 ml), and the mixture was stirred at room temperature for 30 minutes. This was doprwise added to 4-aminopyridine (0.94 g) and triethylamine (2.02 g) dissolved chloroform (50 ml) and acetonitrile (50 ml). The mixture was stirred at room temperature for 30 minutes, thereafter, 10 % potassium carbonate aqueous solution (10 ml) was added, and extraction was carried out with chloroform. The organic solvent layer was washed with saturated aqueous sodium chloride, was dried with Glauber's salt, and the solvent was eliminated by distillation under reduced pressure. The residue was purified with silica gel column chromatography (Wakogel C-200, 60 g). Elution was carried out with a mixed solvent made of methanol (2 pts.) and chloroform (98 pts.), and N-(3'-chlorobenzoyl)-4-aminopyridine (2.21 g) was obtained.

mp: 182-183° (re-crystallised from chloroform–n-hexane).

IRν^{KBr}_{max} (cm^{-1}): 1680, 1600.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 7.36-7.90 (m, 6H), 8.16 (s, 1H), 8.49-8.61 (m, 2H).

Elemental analysis:	Calculated (as $C_{12}H_9N_2ClO$)	C: 61.94, H: 3.90, N: 12.04
	Measured value	C: 61.79, H: 3.82, N: 11.94

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Example 4

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent made of chloroform (50 ml) and acetonitrile (50 ml), thereto was dropwise added 4-chlorobenzoyl chloride (1.75 g), and the mixture was stirred at room temperature for 30 minutes. Thereto was added 10 % potassium carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. The chloroform layer was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was re-crystallised from chloroform–n-hexane, and N-(4'-chlorobenzoyl)-4-aminopyridine (2.20 g) was obtained.

mp: 207-208° (re-crystallised from chloroform–n-hexane).

$IR\nu^{KBr}_{max}$ (cm^{-1}): 1680, 1595.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 7.48 (d, J = 8.6 Hz, 2H), 7.54-7.66 (m, 2H), 7.82 (d, J = 8.6 Hz, 2H), 8.00 (s, 1H), 8.50-8.60 (m, 2H).

Elemental analysis:	Calculated (as $C_{12}H_9N_2ClO$)	C: 61.94, H: 3.90, N: 12.04
	Measured value	C: 61.98, H: 3.92, N: 12.13

Example 5

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent made of chloroform (50 ml) and acetonitrile (50 ml), thereto was added 2-bromobenzoyl chloride (2.19 g), and the mixture was stirred at room temperature for 30 minutes. Thereto was added 10 % potassium carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. The organic layer was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was re-crystallised from chloroform–n-hexane, and N-(2'-bromobenzoyl)-4-aminopyridine (2.56 g) was obtained.

mp: 186-187° (re-crystallised from chloroform–n-hexane).

$IR\nu^{KBr}_{max}$ (cm^{-1}): 1690, 1600.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 7.23-7.70 (m, 6H), 8.40-8.52 (m, 2H), 8.68 (s, 1H).

Elemental analysis:	Calculated (as $C_{12}H_9N_2BrO$)	C: 52.01, H: 3.27, N: 10.11
	Measured value	C: 52.30, H: 3.42, N: 10.13

Example 6

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent made of chloroform (50 ml) and acetonitrile (50 ml), thereto was added 3-bromobenzoyl chloride (2.19 g), and the mixture was stirred at room temperature for 30 minutes. Thereto was added 10 % potassium

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carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. The liquid extract was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was re-crystallised from chloroform–n-hexane, and N-(3'-bromobenzoyl)-4-aminopyridine (2.50 g) was obtained.

mp: 189-190° (re-crystallised from chloroform–n-hexane).

IRν^{KBr}_{max} (cm^{-1}): 1680, 1600.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 7.36 (t, J = 7.6 Hz, 1H), 7.55-7.88 (m, 4H), 7.97-8.05 (m, 1H), 8.28 (s, 1H), 8.48-8.60 (m, 2H).

Elemental analysis:	Calculated (as $C_{12}H_9N_2BrO$)	C: 52.01, H: 3.27, N: 10.11
	Measured value	C: 52.20, H: 3.31, N: 10.25

Example 7

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent made of chloroform (50 ml) and acetonitrile (50 ml), thereto was added 4-bromobenzoyl chloride (2.19 g), and the mixture was stirred at room temperature for 30 minutes. Thereto was added 10 % potassium carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. The chloroform layer was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was re-crystallised from chloroform–n-hexane, and N-(4'-bromobenzoyl)-4-aminopyridine (2.57 g) was obtained.

mp: 216-217° (re-crystallised from chloroform–n-hexane).

IRν^{KBr}_{max} (cm^{-1}): 1680, 1595.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 7.55-7.84 (m, 6H), 8.03 (s, 1H), 8.50-8.61 (m, 2H).

Elemental analysis:	Calculated (as $C_{12}H_9N_2BrO$)	C: 52.01, H: 3.27, N: 10.11
	Measured value	C: 51.85, H: 3.22, N: 10.01

Example 8

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent made of chloroform (50 ml) and acetonitrile (50 ml), thereto was added 2-fluorobenzoyl chloride (1.58 g), and the mixture was stirred at room temperature for 30 minutes. Thereto was added 10 % potassium carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. The liquid extract was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was re-crystallised from chloroform–n-hexane, and N-(2'-fluorobenzoyl)-4-aminopyridine (2.02 g) was obtained.

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mp: 182-183° (re-crystallised from chloroform–n-hexane).

$IR\nu^{KBr}_{max}$ (cm^{-1}): 1690, 1600.

^1H-NMR ($CDCl_3$, 100 MHz) δ: 7.09-7.66 (m, 5H), 8.47-8.58 (m, 2H), 8.71 (s, 1H).

Elemental analysis:	Calculated (as $C_{12}H_9N_2OF$)	C: 66.66, H: 4.20, N: 12.96
	Measured value	C: 66.48, H: 4.12, N: 12.78

Example 9

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent made of chloroform (50 ml) and acetonitrile (50 ml), thereto was added 3-fluorobenzoyl chloride (1.58 g), and the mixture was stirred at room temperature for 30 minutes. Thereto was added 10 % potassium carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. Thc liquid extract was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was re-crystallised from chloroform–n-hexane, and N-(3'-fluorobenzoyl)-4-aminopyridine (1.96 g) was obtained.

mp: 184-185° (re-crystallised from chloroform–n-hexane).

$IR\nu^{KBr}_{max}$ (cm^{-1}): 1690, 1590.

^1H-NMR ($CDCl_3$, 100 MHz) δ: 7.20-7.78 (m, 6H), 8.20 (s, 1H), 8.51-8.62 (m, 2H).

Elemental analysis:	Calculated (as $C_{12}H_9N_2OF$)	C: 66.66, H: 4.20, N: 12.96
	Measured value	C: 66.56, H: 4.12, N: 12.75

Example 10

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent made of chloroform (50 ml) and acetonitrile (50 ml), thereto was added 4-fluorobenzoyl chloride (1.58 g), and the mixture was stirred at room temperature for 30 minutes. Thereto was added 10 % potassium carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. The liquid extract was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was re-crystallised from chloroform–n-hexane, and N-(4'-fluorobenzoyl)-4-aminopyridine (1.98 g) was obtained.

mp: 185-186° (re-crystallised from chloroform–n-hexane).

$IR\nu^{KBr}_{max}$ (cm^{-1}): 1685, 1605.

^1H-NMR ($CDCl_3$, 100 MHz) δ: 7.09-7.26 (m, 2H), 7.56-7.67 (m, 2H), 7.83-7.98 (m, 2H), 8.18 (s, 1H), 8.48-8.60 (m, 2H).

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Elemental analysis:	Calculated (as $C_{12}H_9N_2OF$)	C: 66.66, H: 4.20, N: 12.96
	Measured value	C: 66.52, H: 4.11, N: 12.78

Example 11

3-methoxybenzoic acid (1.52 g), triphenyl phosphine (3.93 g) and carbon tetrabromide (5.32 g) were dissolved in methylene chloride (30 ml), and the mixture was stirred at room temperature for 30 minutes. This was doprwise added to 4-aminopyridine (0.94 g) and triethylamine (2.02 g) dissolved chloroform (50 ml) and acetonitrile (50 ml). The mixture was stirred at room temperature for 30 minutes, thereafter, 10 % potassium carbonate aqueous solution (10 ml) was added, and extraction was carried out with chloroform. The organic layer was washed with saturated aqueous sodium chloride, was dried with Glauber's salt, and the solvent was eliminated by distillation under reduced pressure. The residue was subjected to silica gel column chromatography (Wakogel C-200, 60 g). Elution was carried out with a mixed solvent made of methanol (2 pts.) and chloroform (98 pts.), and N-(3'-methoxybenzoyl)-4-aminopyridine (2.02 g) was obtained.

mp: 104-105° (re-crystallised from chloroform–n-hexane).

IRν^{KBr}_{max} (cm^{-1}): 1680, 1590.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 3.82 (s, 3H), 7.02-7.49 (m, 4H), 7.57-7.69 (m, 2H), 8.43-8.55 (m, 2H), 8.73 (s, 1H).

Elemental analysis:	Calculated (as $C_{13}H_{12}N_2O_2$)	C: 68.41, H: 5.30, N: 12.27
	Measured value	C: 68.58, H: 5.35, N: 12.35

Example 12

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent made of chloroform (50 ml) and acetonitrile (50 ml), thereto was added 4-methoxybenzoyl chloride (1.70 g), and the mixture was stirred at room temperature for 30 minutes. Thereto was added 10 % potassium carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. The organic layer was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was re-crystallised from chloroform–n-hexanc, and N-(4'-methoxybenzoyl)-4-aminopyridine (2.15 g) was obtained.

mp: 139-140° (re-crystallised from chloroform–n-hexane).

IRν^{KBr}_{max} (cm^{-1}): 1665, 1605.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 3.86 (s, 3H), 6.93 (d, J = 9.1 Hz, 2H), 7.55-7.67 (m, 2H), 7.85 (d, J = 9.1 Hz, 2H), 8.43-8.54 (m, 3H).

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Elemental analysis: Calculated (as $C_{13}H_{12}N_2O_2$) C: 68.41, H: 5.30, N: 12.27
Measured value C: 68.32, H: 5.32, N: 12.10

Example 13

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent made of chloroform (50 ml) and acetonitrile (50 ml), thereto was added 2-methylbenzoyl chloride (1.54 g), and the mixture was stirred at room temperature for 30 minutes. Thereto was added 10 % potassium carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. The liquid extract was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was re-crystallised from chloroform–n-hexane, and N-(2'-methylbenzoyl)-4-aminopyridine (2.02 g) was obtained.

mp: 125-126° (re-crystallised from chloroform–n-hexane).
IRν^{KBr}_{max} (cm^{-1}): 1695, 1605.
^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 2.47 (s, 3H), 7.11-7.64 (m, 6H), 8.32-8.44 (m, 2H), 8.61 (s, 1H).
Elemental analysis: Calculated (as $C_{13}H_{12}N_2O$) C: 73.56, H: 5.70, N: 13.20
Measured value C: 73.38, H: 5.61, N: 13.27

Example 14

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent made of chloroform (50 ml) and acetonitrile (50 ml), thereto was added 3-methylbenzoyl chloride (1.54 g), and the mixture was stirred at room temperature for 30 minutes. Thereto was added 10 % potassium carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. The chloroform layer was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was re-crystallised from chloroform–n-hexane, and N-(3'-methylbenzoyl)-4-aminopyridine (1.96 g) was obtained.

mp: 103-104° (re-crystallised from chloroform–n-hexane).
IRν^{KBr}_{max} (cm^{-1}): 1680, 1595.
^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 2.37 (s, 3H), 7.25-7.40 (m, 2H), 7.57-7.74 (m, 2H), 8.40-8.53 (m, 2H), 8.88 (s, 1H).
Elemental analysis: Calculated (as $C_{13}H_{12}N_2O$) C: 73.56, H: 5.70, N: 13.20
Measured value C: 73.38, H: 5.62, N: 13.30

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Example 15

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent made of chloroform (50 ml) and acetonitrile (50 ml), thereto was added 4-methylbenzoyl chloride (1.54 g), and the mixture was stirred at room temperature for 30 minutes. Thereto was added 10 % potassium carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. The chloroform layer was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was re-crystallised from chloroform–n-hexane, and N-(4'-methylbenzoyl)-4-aminopyridine (2.03 g) was obtained.

mp: 180-181° (re-crystallised from chloroform–n-hexane).

IRν^{KBr}_{max} (cm^{-1}): 1670, 1590.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 2.43 (s, 3H), 7.28 (d, J = 8.4 Hz, 2H), 7.56-7.66 (m, 2H), 7.78 (d, J = 8.4 Hz, 2H), 8.25 (s, 1H), 8.46-8.57 (m, 2H).

Elemental analysis:	Calculated (as $C_{13}H_{12}N_2O$)	C: 73.56, H: 5.70, N: 13.20
	Measured value	C: 73.70, H: 5.82, N: 13.27

Example 16

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent made of chloroform (50 ml) and acetonitrile (50 ml), thereto was added 4-cyanobenzoyl chloride (1.65 g), and the mixture was stirred at room temperature for 30 minutes. Thereto was added 10 % potassium carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. The chloroform layer was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was re-crystallised from chloroform–n-hexane, and N-(4'-cyanobenzoyl)-4-aminopyridine (2.07 g) was obtained.

mp: 198-199° (re-crystallised from chloroform–n-hexane).

IRν^{KBr}_{max} (cm^{-1}): 2240, 1695.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 7.54-7.65 (m, 2H), 7.80 (d, J = 8.6 Hz, 2H), 8.00 (d, J = 8.6 Hz, 2H), 8.11 (s, 1H), 8.52-8.62 (m, 2H).

Elemental analysis:	Calculated (as $C_{13}H_9N_3O$)	C: 69.94, H: 4.06, N: 18.83
	Measured value	C: 69.78, H: 3.91, N: 18.80

Example 17

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent made of chloroform (50 ml) and acetonitrile (50 ml), thereto was added 4-t-butylbenzoyl chloride (1.96 g),

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and the mixture was stirred at room temperature for 30 minutes. Thereto was added 10 % potassium carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. The organic layer was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was re-crystallised from chloroform–n-hexane, and N-(4'-t-butylbenzoyl)-4-aminopyridine (2.41 g) was obtained.

mp: 154-155° (re-crystallised from chloroform–n-hexane).

IRν^{KBr}_{max} (cm^{-1}): 1695, 1600.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 1.35 (s, 9H), 7.48 (d, J = 8.6 Hz, 2H), 7.55-7.66 (m, 2H), 7.80 (d, J = 8.6 Hz, 2H), 8.25 (s, 1H), 8.46-8.57 (m, 2H).

Elemental analysis:	Calculated (as $C_{16}H_{18}N_2O$)	C: 75.56, H: 7.13, N: 11.02
	Measured value	C: 75.65, H: 7.32, N: 11.21

Example 18

4-(N,N-dimethylamino) benzoic acid (1.65 g), 2-chloro-1-methylpyridinium iodide (3.82 g), triethylamine (2.02 g) and 4-aminopyridine (0.94 g) were added to methylene chloride (50 ml) and the mixture was stirred at the reflux temperature for 8 hours. Thereto was added 10 % potassium carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. The liquid extract was washed with saturated aqueous sodium chloride solution and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (Wako-gel C-200, 60 g). The purified residue was eluted with a mixed solvent comprising methanol (2 pts.) and chloroform (98 pts.), and N-[4'-(N',N'-dimethylamino) benzoyl]-4-aminopyridine (2.12 g) was obtained.

mp: 219-220°C (re-crystallised from chloroform–n-hexane).

IRν^{KBr}_{max} (cm^{-1}): 1660, 1605, 1590.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 3.06 (s, 6H), 6.68 (d, J = 9.1Hz, 2H), 7.54-7.65 (m, 2H), 7.78 (d, J = 9.1 Hz, 2H), 7.95 (s, 1H), 8.44-8.55 (m, 2H).

Elemental analysis:	Calculated (as $C_{14}H_{15}N_3O$)	C: 69.69, H: 6.27, N: 17.42
	Measured value	C: 69.56, H: 6.15, N: 17.20.

Example 19

2,4,5-trimethoxybenzoate (2.12 g), triphenylphosphine (3.93 g) and carbon tetrabromide (5.32 g) were dissolved in methylene chloride (30 ml), and the mixture was stirred at room temperature for 30 minutes. This mixture was added dropwise to triethylamine (2.02 g) and 4-aminopyridine (0.94 g)

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dissolved in chloroform (50 ml) and acetonitrile (50 ml), and thereafter stirring was carried out at room temperature for 30 minutes. Thereto was added 10 % potassium carbonate aqueous solution (10 ml), and extraction was carried out with chloroform. The chloroform layer was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was purified by silica gel column chromatography (Wako-gel C-200, 80 g) and was eluted from methanol (2 pts.) and chloroform (98 pts.), and N-(2',4',5'-trimethoxy benzoyl)-4-amino pyridine (2.65 g) was obtained.

mp: 167-168°C (re-crystallised from chloroform–n-hexane).

$IR\nu^{KBr}_{max}$ (cm^{-1}): 1675, 1610, 1590.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 3.93 (s, 3H), 3.97 (s, 3H), 4.07 (s, 3H), 6.56 (s, 1H), 7.53-7.64 (m, 2H), 7.76(S, 1H), 8.44-8.57 (m, 2H), 9.98 (s, 1H).

Elemental analysis: Calculated (as $C_{15}H_{16}N_2O_4$) C: 62.49, H: 5.59, N: 9.72

Measured value C: 62.59, H: 5.70, N: 9.79.

Example 20

3,4-dimethoxybenzoic acid (1.82 g), triphenylphosphine (3.93 g) and carbon tetrachloride (5.32 g) were dissolved in methylene chloride (30 ml), and the mixture was stirred at room temperature for 30 minutes. This mixture was added dropwise to triethylamine (2.02 g) and 4-aminopyridine (0.94 g) dissolved in chloroform (50 ml) and acetonitrile (50 ml). Stirring was carried out at room temperature for 30 minutes, and thereafter 10 % potassium carbonate aqueous solution (10 ml) was added, and extraction was carried out with chloroform. The chloroform layer was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was purified by silica gel column chromatography (Wako-gel C-200, 60 g) and was eluted from a mixed solvent comprising methanol (2 pts.) and chloroform (98 pts.), and N-(3',4'-dimethoxybenzoyl)-4-aminopyridine (2.40 g) was obtained.

mp: 149-150°C (re-crystallised from chloroform–n-hexane).

$IR\nu^{KBr}_{max}$ (cm^{-1}): 1650, 1580.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 3.91 (s, 3H), 3.93 (s, 3H), 6.88 (d, J = 8.5Hz, 1H), 7.45 (dd, J = 2Hz and 8.5Hz, 1H), 7.48 (d, J = 2Hz, 1H), 7.57-7.68 (m, 2H), 8.45-8.56 (m, 3H).

Elemental analysis: Calculated (as $C_{14}H_{14}N_2O_3$) C: 65.10, H: 5.46, N: 10.85

Measured value C: 65.30, H: 5.55, N: 10.91.

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Example 21

2,6-dimethoxybenzoic acid (1.82 g), triphenylphosphine (3.93 g) and carbon tetrabromide (5.32 g) were dissolved in methylene chloride (30 ml), and the mixture was stirred at room temperature for 30 minutes. This mixture was added dropwise to triethylamine (2.02 g) and 4-aminopyridine (0.94 g) dissolved in chloroform (50 ml) and acetonitrile (50 ml). Stirring was carried out at room temperature for 30 minutes, and thereafter 10 % potassium carbonate aqueous solution (10 ml) was added, and extraction was carried out with chloroform. The organic layer was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, the residue was purified by silica gel column chromatography (Wako-gel C-200, 70 g) and was eluted from a mixed solvent comprising methanol (2 pts.) and chloroform (98 pts.), and N-(2',6'-dimethoxybenzoyl)-4-aminopyridine (2.40 g) was obtained.

Mp: 218-219°C (re-crystallised from chloroform–n-hexane).

IRν^{KBr}_{max} (cm^{-1}): 1690, 1600.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 3.82 (s, 6H), 6.58 (d, J = 8.3Hz, 2H), 7.32 (t, J = 8.3 Hz, 1H), 7.50-7.60 (m, 2H), 8.05 (s, 1H), 8.39-8.49 (m, 2H).

Elemental analysis:	Calculated (as $C_{14}H_{14}N_2O_3$)	C: 65.10, H: 5.46, N: 10.85
	Measured value	C: 65.32, H: 5.65, N: 10.93.

Example 22

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent comprising chloroform (50 ml) and acetonitrile (50 ml), and thereto was added 2,6-dichlorobenzoyl chloride (2.09 g), and the mixture was stirred at room temperature for 30 minutes. 10 % potassium carbonate aqueous solution (10 ml) was added, and extraction was carried out with chloroform. The liquid extract was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, The obtained residue was recrystalliscd from chloroform-methanol-n-hexane, and N-(2'6'-dichlorobenzoyl)-4-aminopyridine (2.53 g) was obtained.

mp: >250°C (re-crystallised from chloroform-methanol-n-hexane).

IRν^{KBr}_{max} (cm^{-1}): 1700, 1600.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 7.32-7.41 (m, 3H), 7.65-7.76 (m, 2H), 8.39-8.50 (m, 2H).

Elemental analysis:	Calculated (as $C_{12}H_8N_2Ocl_2$)	C: 53.95, H: 3.02, N: 10.49
	Measured value	C: 53.75, H: 2.95, N: 10.45.

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Example 23

4-aminopyridine (0.94 g) and triethylamine (2.02 g) were dissolved in a mixed solvent comprising chloroform (50 ml) and acetonitrile (50 ml), and thereto was added 4-nitrobenzoyl chloride (1.85 g), and the mixture was stirred at room temperature for 30 minutes. 10 % potassium carbonate aqueous solution (10 ml) was added, and extraction was carried out with a mixed solvent comprising chloroform (90 pts.) and methanol (10 pts.). The organic layer was washed with saturated aqueous sodium chloride and was dried with Glauber's salt. The solvent was eliminated by distillation under reduced pressure, The obtained residue was recrystallised from chloroform-methanol-n-hexane, and N-(4-nitrobenzoyl)-4-amino pyridine (1.56 g) was obtained.

mp: 245-247°C (re-crystallised from chloroform-methanol-n-hexane).

IRν^{KBr}_{max} (cm^{-1}): 1685, 1605, 1520, 1340.

^{1}H-NMR ($CDCl_3$, 100 MHz) δ: 7.73-7.84 (m, 2H), 8.13 (d, J = 8.6Hz, 2H), 8.34 (d, J = 8.6 Hz, 2H), 8.40-8.51 (m, 2H).

Elemental analysis:	Calculated (as $C_{12}H_9N_3O_3$)	C: 59.26, H: 3.73, N: 17.28
	Measured value	C: 59.10, H: 3.65, N: 17.05.

Pharmacological test

Test method

The physiological activity of the drugs of this invention was investigated by a process using the atria isolated from guinea pigs.

Using both genders of guinea pigs of 300-400 g body weight, the animals were caused to faint by hitting the head part and were bled to death, thereafter, the heart was isolated and atrium was cut out. The tips of left and right artial auriculae were tied with thread,and were suspended in an organ bath filled with Krebs-Henseleit liquid (liquid temperature of 32°C), and 95% O_2-5% CO_2 was bubbled through. Contractile force of atrium was measured isometrically using isometric transducer. After the movement of atrium had stabilised, the compound of this invention of formula (I) was added to the organ bath. The compound of this invention of formula (I) concentration-dependently increased the contractile force. The drug concentrations at which the contractile force was increased by 20 % or 50 % were shown in the Table below.

EC20 and EC50 respectively denote the molar concentrations at which the atrial contractile force was increased by 20 % and 50%.

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R	EC_{20}	EC_{50} (g /ml)	
H	2.4	*	(note 1)
2'-Cl	0.52	*	
3'-Cl	1.2	4.9	
4'-Cl	0.83	4.8	
2'-Br	2.2	*	
3'-Br	1.5	4.5	
2'-F	3.0	*	
3'-F	0.49	4	
4'-F	1.3	12	
3'-OCH_3	0.4	2.6	
4'-OCH_3	0.16	8.1	
3'-CH_3	0.62	2.5	
4'-CH_3	0.45	7.4	
4'-CN	1.8	9	
4'-tertBu	0.45	1.5	
4'-$N(CH_3)_2$	2.8	*	
2',4',5'-triOCH_3	0.96	4.2	
3',4'-diOCH_3	0.63	*	

Note 1 contractive force increase did not reach to 50 %.

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